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How do we manage over diagnosis/over treatment in breast screening?

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Abstract:	Over diagnosis is the inevitable flip side of early detection resulting in unnecessary labelling of well women with a diagnosis of cancer and possible unnecessary treatment. Over diagnosis occurs because breast cancers have different rates of growth and slow growing cancers are preferentially detected by screening. Some of these slow growing screen-detected cancers may never have been clinically apparent during an individual's lifetime. Evaluating the benefits and risks of screening are complex but this has been performed for the UK population by an independent review led by Professor Marmot. It might be possible to limit over diagnosis by Identifying women with "low risk disease" earlier either at the point of screening when additional investigations could be delayed (possibly for ever) so that they are not subjected to additional diagnostic tests, or at the point of diagnosis. Both these options would require major re-education of clinicians and the public who would need to accept that screening is 'deliberately ignoring a cancer' There is a long surgical history of reducing the burden of treatment which continues today with trials of management of the axilla and reducing or even omitting radiotherapy for low risk disease. The Low Risk Ductal Carcinoma in situ trial (LORIS) has started to Identify a group of breast cancer patients who could avoid surgery and be offered active monitoring. We need to consider planning a similar trial for row risk invasive breast cancer.

How do we manage over diagnosis/over treatment in breast screening?

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Author Contributions

	MGWallis
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Editor, Clinical Radiology

Dear Sir

I would like to thank the referees for their complimentary review.

My responses alterations are detailed below

1 EDITOR'S COMMENTS:

1.1 If you could please just check the refs and language that would be great.

These have both been amended as requested.

There are a number of places ‘word’ has suggested simplification but in most cases I think this loses the sense of the statement.

1.2 Personally I would leave the figures as they are; I think the visual impact is much better than the written word; if you wish to shorten the text instead then fine - if not then I'm happy either way. I will leave to your discretion.

I have left the figures and their captions alone and I have not substantially altered the main text. I am happy to do this but I am within word limit and when teaching trainees (and colleagues) I find that they have difficulty with these concepts so repetition is no bad thing. When I read papers I find it really helpful if the main text and the figures each ‘stand-alone’ provided it is not just repetition

2 EDITORIAL OFFICE REQUIREMENTS:

Please add your Figure Legend to the main manuscript file, beneath your References.

Done

3 REVIEWERS' COMMENTS:

Reviewer #1:

3.1 There are minor typographical errors in the main body of the review which are easily addressed

Please see 1.1

3.2 however more frequent typographical/formatting errors are noted in the references which require checking and amending. e.g. number 23-. Waller J, Whitaker KL, Winstanley K,Power E, Wardle J. A survey of womens responses to information about over diagnosis in breast cancer screening in Britain Br J Cancer 2014;1111:1831-1835 doi 10.1038/bjc.2014.482-2 errors in title.

ref number 8 has an additional "and" in the title

Please see 1.1

3.3 Figures 2 and 3 are nice diagrammatic representations but the concepts are well explained in the text and I don't think they add anything to the review.

Please see 1.2

Abstract

Over diagnosis is the inevitable flip side of early detection resulting in unnecessary labelling of well women with a diagnosis of cancer and possible unnecessary treatment.

Over diagnosis occurs because breast cancers have different rates of growth and slow growing cancers are preferentially detected by screening. Some of these slow growing screen-detected cancers may never have been clinically apparent during an individual's lifetime. Evaluating the benefits and risks of screening are complex but this has been performed for the UK population by an independent review led by Professor Marmot.

It might be possible to limit over diagnosis by Identifying women with "low risk disease" earlier either at the point of screening when additional investigations could be delayed (possibly for ever) so that they are not subjected to additional diagnostic tests, or at the point of diagnosis. Both these options would require major re-education of clinicians and the public who would need to accept that screening is 'deliberately ignoring a cancer'

There is a long surgical history of reducing the burden of treatment which continues today with trials of management of the axilla and reducing or even omitting radiotherapy for low risk disease. The Low Risk Ductal Carcinoma in situ trial (LORIS) has started to Identify a group of breast cancer patients who could avoid surgery and be offered active monitoring. We need to consider planning a similar trial for row risk invasive breast cancer.

Over diagnosis: disease detected that, in the absence of screening, would not otherwise have become clinically apparent and would not have had any adverse consequences on the individual. This is a highly charged political issue to the extent that the BMJ now runs an annual international conference. (1) Dr Margaret McCarthy a Scottish General Practitioner and lead writer for the BMJ summarised the issue in 2007. 'Too much testing of well people and not enough care for the sick worsens health inequalities and drains professionalism, harming both those who need treatment and those who don't. (2)

Screening for breast cancer continues to be mired in debate. The benefit in terms of mortality reduction seems to have been settled (3-5) even if its magnitude and who to screen is less clear. The over diagnosis debate summed up in 2009 by Gilbert Welsh (6) "the question is no longer whether it occurs but how often it occurs" has not been resolved by the 'independent reviews' summarised by Houssami (7) and there are continuing contradictory new publications (8,9).

Why does over diagnosis occur at screening?

Breast cancer is not one disease with a uniform growth rate (Figure 1). Screening finds both fast and slow growing cancers. The periodic nature of screening means that the faster growing cancers (those with a worse prognosis that are likely to progress to metastatic disease) are less likely to be found at screening and have a greater tendency to appear between screens (interval cancers). The lower grade and slower growing cancers are much more likely to be picked up by screening; length bias. (figure 2) (10). These cancers are more likely to be over diagnosed because the preclinical, screen-detected cancer is progressive but the person dies prematurely of another cause before the time at which symptoms would have occurred or the growth rate of a truly progressive cancer is not rapid enough to give rise to symptoms during the person's life time. It is also possible that a cancer stops growing and becomes indolent for some reason or possibly even regresses (11) but this is, to say the least, controversial (12). Additionally, the slower growing cancers tend to produce more of a stromal reaction so they are easier to perceive on mammography (13)

The paradox for the clinician providing breast screening is that detecting 'early' breast cancer leads to mortality reduction so they are encouraged and incentivised to find more 'early' cancers even if some of these might never have become clinically apparent or trouble the patient so over diagnosis and early detection are the two sides of the same coin.

The difficulty for individual treating clinicians and patients is that for any one individual patient we cannot readily distinguish who has been 'saved' by screening and early treatment and who has been harmed by unnecessary labelling with a lifelong diagnosis, unnecessary treatment and its side effects (figure 3). So, we are left with Gray and Raffle's popularity paradox. "The greater the harm through over diagnosis and overtreatment from screening, the more people there are who believe they owe their health, or even their life, to the programme." (14)

Quantifying both the benefits of screening in terms of reducing mortality from breast cancer and the risk of over diagnosis is complex and over many years the discussion has become polarised with quoted rates of over diagnosis between 1 and 2% (15) and 52% (16). The UK government responded to public pressure in October 2013 and jointly commissioned an independent review with Cancer Research UK. This review was performed by a panel of independent experts who had never previously published about breast screening and was chaired by Prof MG Marmot (4).

In theory, the debate should be relatively simple to resolve using the randomised controlled trials. The excess of cancers diagnosed into the intervention arm (screening) should be balanced by the excess of cancers in the control group after the trial has finished. The problem is that in real-life this has never happened as screening does not stop. So, the magnitude of the effect must be "calculated" by a variety of epidemiological and statistical tools using observational data, historical data and geographical controls. As the effect on mortality seems to continue long after the trial has ended (17) each estimate ~~has to~~ must decide how long to wait for the excess cancers to be balanced out. The shorter the period (18) the larger the estimate of over diagnosis and the longer the period of surveillance the smaller the estimate (19).

It is beyond the scope of this article to consider in any detail the statistical and epidemiological complexities behind the calculations particularly as this was performed in ~~great~~ detail by the Marmot Review (4).

Estimating the benefits of screening:

How good are the estimates of benefits? Ignoring the statistical confidence in the actual numbers, all the randomised controlled trials are old and treatment has improved so their relevance to 'today's practice' is debated. There are well rehearsed arguments about the randomisation methodology and imperfections and disagreements about what outcome should be measured. The trials were initially designed and powered to measure breast cancer specific mortality but this can be biased by how accurately the cause of death is recorded and how/if this was validated. Reductions in overall mortality are very small and depend on length of follow up. Finally, how is the risk reduction presented? Should the benefit be expressed in terms of the whole population (clearly important to any potential funders of screening), namely the benefit of sending the invitation or should the benefit be expressed in terms of ~~actually~~ attending the screening appointment which is higher (5). This is a figure that is of more use to the individual woman concerned about balancing the harms and benefits of attending her appointment.

Estimating over diagnosis

The complexity of estimating the degree of over diagnosis is even harder. Carter (20) identified four types of study: follow-up of randomised controlled trials, pathology and imaging follow up, modelling and epidemiological cohort studies. He concluded that the need for ~~a~~ well-designed ecological and cohort studies in multiple settings, underpinned by internationally agreed standards and unbiased researchers. De Gelder (21) describes seven separate methodologies: these including inclusion or exclusion of DCIS, using the screening age range or the woman's lifetime and finally whether the rate of over diagnosis is related to the women invited, the women screened or even the cancers detected. Once again this is covered in considerable detail by the Marmot review (4).

Once a relative risk has been “agreed” then this needs to be translated to the individual screening programme and the population it serves. This will vary because of the interval between screens and the intrinsic risk of a population being offered screening. The specific risk groups selected, age and personal family history being the most obvious, but in some populations as well as opportunistic programmes background density is being used to select specific women for additional imaging (22). Finally screening performance is dependent on the test(s) being used and the professionals implementing and interpreting them.

The balance of harm and benefit.

Having taken all these issues into account the Marmot review (4) came up with a set of figures specifically related to the United Kingdom based on their meta-analysis of 11 randomised controlled trials with 13 years of follow-up. They estimated a 20% (11 to 20%) reduction in breast cancer mortality for women invited to screening over a 20-year period. By applying this reduction to the National Breast Screening Programme in the United Kingdom they estimated that one breast cancer death would be prevented for every 235 women invited to screening and that 180 women would need to be screened to prevent one breast cancer death. The panel acknowledged that there is uncertainty around these numbers and concluded that the estimates of benefits would be in the range of one breast cancer death prevented for approximately 250 women invited. In 2013 at the time of the report they considered that that corresponded two approximately 1300 deaths from breast cancer being prevented each year or 22,000 years of life saved. They balanced this against the risk of over diagnosis which they estimated to be at approximately 19% of the cancers diagnosed based on a 20-year programme.

This translated into notional figures for 10,000 women invited to screening from the age of 54 over a 20-year period. Estimating that 681 breast cancers (invasive and DCIS) will be diagnosed, 129 of these will represent over diagnosis and 43 deaths from breast cancer will be prevented.

As well as deciding what is truly 'balanced' information the public understanding of over diagnosis and risk is complex (23). There is a need to provide this information in an understandable form. Fig 4 (24) is one of the many pictograms available from the UK. Hersch (25) developed a similar tool and tested the effects in an Australian population. At telephone interview 3 weeks after the intervention more women receiving the tool felt able to make an informed choice when compared to the control group. The intervention also improved knowledge about screening and breast cancer risk. However, it did lead to a reduction in positive attitudes to breast screening and a reduction in the number of women intending to attend screening over the next 2 to 3 years. Longer follow up and impact on attendance is awaited. (25)

The consequences of over diagnosis are the psychosocial effect of being labelled with a diagnosis of breast cancer (26) and the burden of unnecessary treatment. The problem is that we cannot currently distinguish which of these 681 individual women diagnosed with screen detected breast cancer will be lucky enough to be one of the 43 whose death from breast cancer has been prevented and which are the 129 who have been overtreated as neither group dies from cancer. As we have very little data on the natural history of untreated breast cancer it is a major challenge to use historical data, based on women having received conventional treatment, to separate these two groups into the ones who are cured and the ones who did not require treatment in the first place.

This leaves three potential approaches,

Reducing over diagnosis by

- Identifying women with "low risk disease" earlier either at the point of screening when additional investigations could be delayed (possibly for ever) so that they are not subjected to additional diagnostic tests, labelled with a diagnosis of cancer and offered treatment.

Reducing treatment by

- De-escalation of treatment for all women or at least those perceived to be at low risk,

- Identifying a group of breast cancer patients who could avoid surgery and be offered active monitoring

Reducing over diagnosis.

The principle group at risk of over diagnosis is the older woman. The older the age at detection the more likely she is to have a cancer diagnosis that would either not present or not cause problems within her life. AgeX, a nationwide cluster randomization of extending the NHS Breast Screening Programme began as a trial of additional screening at ages 47-49 and at ages 71-73, now has ethical approval to continue triennial invitations at ages 71-76 or at ages 71-79 thereby assessing the effects of continuing triennial screening for several years after age 70 (27).

Using radiological features to predict risk is not foreign to radiology with well recognised guidelines for the management of incidental nodules identified at CT scanning (28). Tabar has documented the common mammographic features associated with high grade invasive cancers (29) and Alexander with low grade invasive cancers (30) but using this to reduce the number of recalls or identifying cancers not to investigate has never been part of the screening programme culture mainly because our current technology and knowledge is not good enough to perform this task with enough specificity or certainty. This dilemma is best illustrated by the problem of microcalcification. The majority of calcification that we biopsy turns out to be benign and the more we identify and biopsy the larger number of 'incidental' pathological risk or low risk malignant lesions are found (31) however this should be balanced against the fact that a few of these lesions contain small high grade invasive disease (the cancers we really need to pick up). High rates of DCIS detection are associated with higher rates of small high-grade invasive cancer detection (32,33) and lower interval cancer rates (31)

Artificial intelligence, machine learning and big data sets are seen to be one way forward (34, 35). Currently the emphasis is to improve the predictive accuracy of screening by reducing the recall rate

to reduce harm (36). Even if they ~~were able to~~ could dichotomise mammographic abnormalities by risk with potential support from functional imaging which preferentially images metabolically active disease (37), the whole ethos and purpose of screening would need to be changed.

Radiologists and screen readers are performance monitored by their cancer detection rates (38) and haunted by their missed cancers if not hunted through the legal system with fears of missing a diagnosis and of litigation being a major cause of both over investigation and thus over diagnosis (39)

With the exception of tomosynthesis, which can reduce recall as well as increasing cancer detection (40) new technology for screening or supplemental screening for higher risk women is always introduced to find more cancer (41). Unfortunately, early publications do not have long enough follow up to report interval cancers and do not usually make any effort to distinguished high risk from low risk disease. Reporting more small cancers and fewer node positive cancers (probably those most likely to be over diagnosed) is not a proper substitute for reporting grade and biological marker characteristics.

Patient expectation and knowledge will need a radical overhaul as we will need to explain that screening is not about finding cancer but about finding killing cancer which means that in the very extreme scenario an abnormality is identified either by the film reader or machine reader that looks like a low risk cancer and it is just ignored and allowed to grow on the principle 'that what you don't know about can't harm you'. Alternatively, the woman is recalled to explain that she probably does have a cancer but its' not an 'important one' so we do not intend to confirm this by biopsy or other imaging, which might throw up another 'false positive' lesion, we are just going to recommend active monitoring. At least in this case the woman can make an informed choice.

Reducing over treatment.

De-escalation of treatment is not new and there has been a long and distinguished history of progressive reduction in the aggressiveness of surgical treatment of breast cancer. Fisher showed that, after 25 years of follow up, radical mastectomy offered the same survival as simple mastectomy (42). He further showed in NSABP -06 that, at 20 years, local surgery with radiotherapy was equivalent to mastectomy, for invasive cancer less than 4 cm in size (43). In more recent years the recommendations for the amount of normal breast tissue surrounding a cancer (surgical margin) has steadily reduced (44).

Management of the axilla has similarly changed. Removal of all axillary nodes via axillary lymph node dissection (ALND) was considered to be standard treatment (45) but is associated with significant morbidity (46). It was replaced by Sentinel Lymph Node Biopsy (SLNB) (47,48) and then in 2011 the ACOSOG Z001115 trial (49) showed that in a specific group of women with a low burden of axillary disease identified at sentinel lymph node sampling they do not gain any additional benefit from proceeding to therapeutic axillary node clearance. Although there is still controversy regarding the results and other trials are currently in progress (50) this trial has revolutionised the management of the axilla. Unfortunately, guidance for Pre-operative staging of the axilla has not caught up (51) and routine staging with ultrasound and needle biopsy of abnormal nodes has led to reports of between 38% (52) and 47%(53) of women with positive nodes on needle biopsy being over treated with ALND.

The addition of radiotherapy after conservation surgery reduces relapse rate by about half and mortality by a sixth (54) but at the cost of significant side effects including cardiac toxicity and up to a third of women reporting long term cosmetic problems. (55). Reducing the number and duration of treatments to deliver the same dose from 5 weeks to 3 weeks and more recently 1 week reduces side effects without effecting outcomes however the results of accelerated partial breast radiotherapy are less clear cut. (57). Given that current local recurrence rates are so low the most

recent trial to be launched is PRIMETIME a case cohort study which is adding a single proliferation marker to standard clinical features, ER PR and HER2 to identify women at very low risk of local recurrence who will receive a recommendation to omit radiotherapy (55)

Identifying a group of breast cancer patients who could avoid surgery and be offered active monitoring

DCIS has been described as a disease of screening (18), as it classically present as mammographic calcifications rather than a mass lesion and it is considered to be a non- obligate precursor of invasive cancer with an unknown course of progression. When treated it has a very low breast cancer specific mortality (57). The addition of radiotherapy after local surgery reduces local recurrence rates (58), particularly in women with close margins (59). Of those women who have subsequent events nearly half are invasive and there is some evidence that death from breast cancer although rare is usually/always preceded by an invasive event (57). The challenge is to identify those women with DCIS who are unlikely to recur or alternatively find a marker which can predict recurrence at diagnosis or predict recurrence before it becomes a risk for death. More recent prognostic scores to determine who will benefit from radiotherapy require validation if they are to gain widespread acceptability. (60)

Histopathology currently divides DCIS into three grades on morphological grounds and there is good evidence that low-grade disease recurs late (61) and more frequently as low grade invasive cancer (62-64) and that if a higher grade invasive disease occurs it is likely to be a new primary. This is supported by Sagara using the SEER database (65) who showed no significant survival benefit of breast surgery for low-grade DCIS with a 10-year overall survival of 91% in the non-surgery group and 87.9% in the surgery group and 10-year breast cancer specific survival of 93.4% in the non-surgery group and 98.8% in the surgery group.

Histopathological grading is not perfect (66-68) and at least in trials investigating the benefits of radiotherapy and hormone treatment, which might of course have biased selection, there does

seem to be a difference in grading between countries with the USA and Europe having larger numbers of lower grade disease than in the UK screening programme. (69-70)

This epidemiological evidence is now supported by genomic and transcriptional evidence. The traditional model of breast cancer progression with increasing numbers of molecular activation of oncogenes and inactivation of suppressor genes has now been shown to be a great deal more complex with different multiclonal evolutions being related to specific metastatic sites (71) There is now increasing evidence that there are likely to be 2 distinct evolutionary pathways for low and high-risk disease. A low risk pathway: Flat epithelial atypia /atypical ductal hyperplasia/low grade DCIS /low grade invasive disease pathway primarily characterised by frequent loss of 16q. A high-risk pathway: High grade DCIS progressing to high grade invasive disease where there is infrequent loss of 16q accompanied by more complex changes with frequent loss of 13q with multiple high-level gene amplification (72)

Internationally the breast cancer community has taken the plunge and followed the example of urologists treating prostate cancer (the ProtecT trial) (73). In the UK the Low RISk DCIS trial (LORIS) recruiting its first patient in October 2014 (74), LOw Risk DCIS (LORD) in the Europe (75) and Comparison of Operative to Monitoring and Endocrine Therapy for Low Risk DCIS (COMET) in the America (76) are open for recruitment. The trials are fundamentally similar recruiting women with "low risk" DCIS presenting with microcalcification and offering randomisation to conventional surgical treatment verses active monitoring with primary outcomes of ipsilateral breast cancer free survival at a variety of time points.

These trials have not been simple to set up, like ProtecT (73) before it, they have been slow to recruit in the initial stages as the medical profession need to change ingrained behaviour of offering surgery and patients have been brought up to expect "cancer" to be removed. (77) It is difficult to sell the concept that active monitoring is about avoiding treatment until it is necessary and that treatment at that point can be offered when cure can still be offered. Providing safety nets for both

professionals and patients is key to success without excluding too many to make recruitment impossible or making follow-up so intrusive that the primary surgery would have been preferable.

Securing a solid diagnosis at presentation prior to randomisation relies on biopsy techniques that provide adequate material to reduce the risk of missing something serious (in the case of microcalcification high grade or invasive disease). Each trial has a different strategy to reduces this risk, all requiring vacuum assisted biopsy but LORIS, the UK trial, has added central pathology review so that at least there is consistency in the diagnosis of "low risk" disease. The hardest paradox is the presence of extensive calcification where on one hand there is professional anxiety about missing high grade DCIS or an invasive cancer somewhere in the area of concern verses the fact that the patient concerned has the "most to lose" in terms of the conventional extensive surgical options including mastectomy.

Active monitoring is equally hard to balance as there is no good evidence about how these lesions change over time, presumably they will grow but this is not necessarily a predictor of progression to invasion, so a balance must be drawn between continuous monitoring verses regular intervention with further biopsies. All trials have defined criteria for intervention to reduce the chances that active monitoring by mammography does not turn into active monitoring by vacuum assisted biopsy.

As the three trials will provide a cohort of women managed without surgery Cancer Research UK and Dutch Cancer Society has funded a joint project preventing unnecessary breast cancer treatment PRECISION (78) to trying to identify imaging, biological and genetic markers for risk of recurrence from a series of historical treated cohorts that will then be prospectively validated in the new trials.

Having committed to no surgical trials for DCIS the next step is to consider future trials for 'low risk' invasive cancer. We have good follow up data suggesting conventional treatment of tubular cancers is associated with an excellent prognosis. In Rakha's series of 102 cases all distant recurrences followed on from the development of a second higher grade cancer (79). We also know that local recurrence rates are now very low (55) and adding proliferation markers to conventional markers

could well increase confidence. Just leaving these cancers to active monitoring is one choice. Minimally invasive image guided percutaneous ablation is still in its infancy but there are multiple small trials, with a wide range of tumour sizes, suggesting high rates of technical success with low complication rates but only 75% 'complete ablation'. (80). We must of course resist the temptation to replace relatively simple low risk surgery with expensive high technology imaging because we can.

What do we need to do to prepare for this brave new world?

Firstly, we need to be open and honest about the screening programme and start to change the pervasive publicity around cancer. Personalised medicine is not just about more more more, the new wonder drug and magic bullet it is also about cancer not being one disease, it's a rainbow. We do have new treatments for the red end but there are lots of cancers at the blue end that don't need treating in a hurry, under artificial politically driven waiting time targets, and might need less or even no treatment at all. This is not a new covert way of saving money for social care.

Secondly, we need to ensure that every one of our patients has the opportunity to be involved in a trial, as the late Professor Adele Francis was very fond of telling her surgical colleagues 'it's not good enough to just keep on doing what we have always done'

Finally, we need to optimise the enormous data base that is NBSS, link it to cancer registry and all the digital images stored on PACS and if necessary start storing the 'raw' not for processing data, which is needed for machine learning. Then start using the information to design the trials of the future to maximise benefit and minimise harm.

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Figure captions

Figure 1 Cancers do not all grow at the same rate

Cancer 1: fast growing unlikely to be picked up by screening

Cancer 2: slow growing but progressive will benefit from screening

Cancer 3: very slow growing likely to be over diagnosed and over treated

Cancer 4: non-progressive

Figure 2 Length bias: the fixed time interval between screens means that it is more likely that the slow growing tumours will be detected. The length of the arrows represents the time between detectability at screening and the clinical onset. The grey arrows represent screen detected cancers the black one interval cancers. After Sardanelli (10)

Fig 3 Screening and over diagnosis: Comparison of line A (no screening) and line B (screening) shows a clear increase in survival not only because of early diagnosis but prolongation of life. Line C (over diagnosis) the over diagnosis is clear cut if an individual dies from other causes before the 'point of clinical onset' but death from other causes after this point could either be the result of successful treatment or over diagnosis of a 'non-killing' cancer.

Figure 4: Pictogram from 'Breast Cancer Now' showing breast screening key facts (24)

Figure 1

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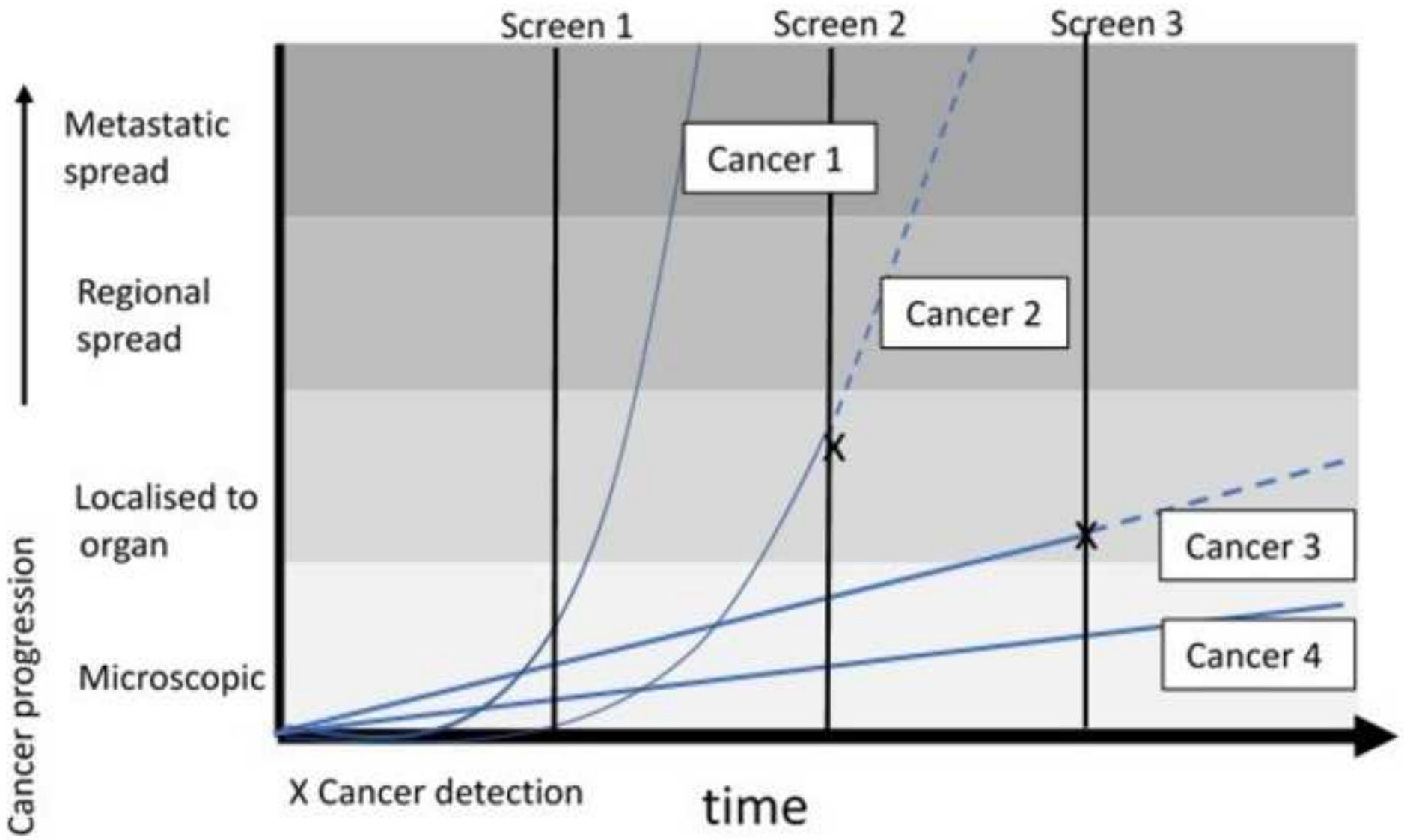

Figure 2

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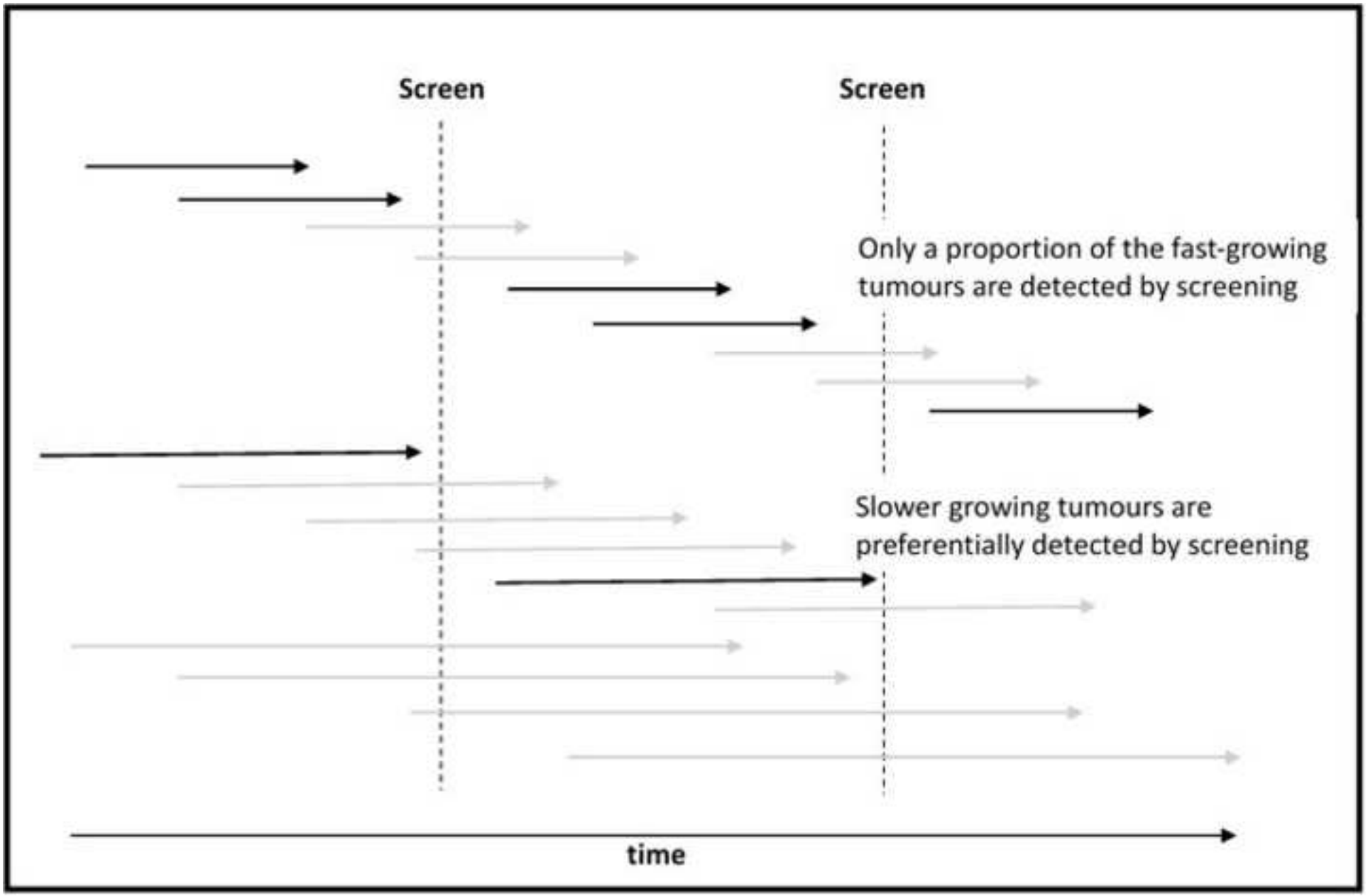

Figure 3

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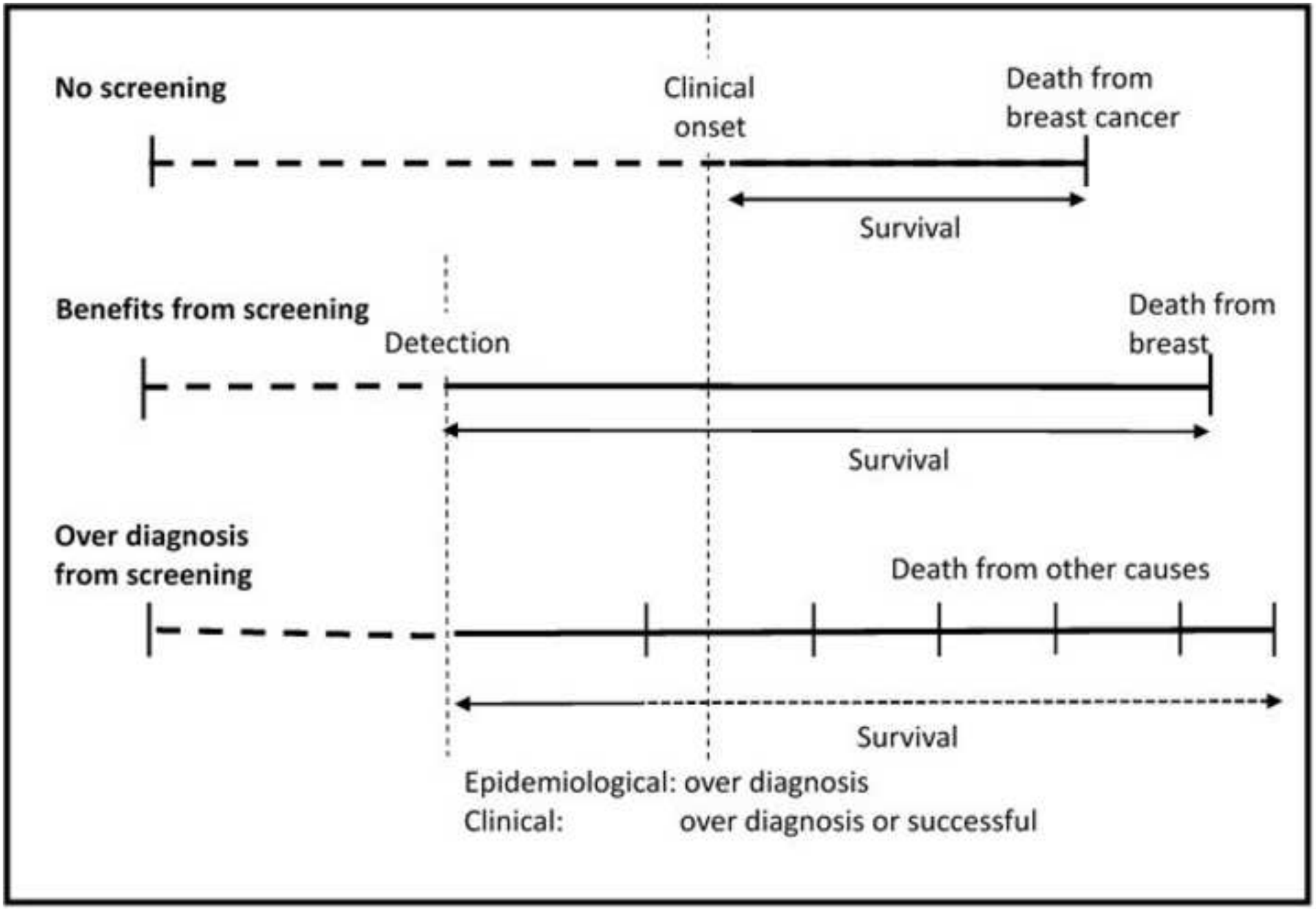

Figure 4

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